W. Davis
09/781,023

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=> dis his

     (FILE 'HOME' ENTERED AT 14:33:05 ON 10 AUG 2001)

     FILE 'CAPLUS' ENTERED AT 14:33:40 ON 10 AUG 2001
               E APC/CT 5
               E CACHEXIA/CT 5
L1         14916 S E3+ALL/CT
               E CANCER/CT 5
L2          7033 S E3
               E IMMUNE RESPONSE/CT 5
               E HEAT SHOCK PROTEIN/CT 5
               E URINE/CT 5
L3        224418 S E3+ALL/CT

=> file reg;s cachexia/cn
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                              33.61      33.76

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for details.


L4             0 CACHEXIA/CN

=> fil medl,caplus,biosis,embase,wpids,jicst;s (urine or ?uria?) and
(immune(w)(response or stimulat?) or bacteria cell wall extract or heat shock
protein)
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                               4.11      37.87

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Prepared by M. Hale 308-4258

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SEARCH ENDED BY USER
SEARCH ENDED BY USER

=> s (l1 or cachexia or cancer or tumour or tumor or l2 or neoplasm?) and (l3
or urine or ?uria?) and (immune(w)(response or stimulat?) or bacteria cell
wall extract or heat shock protein)
L6          76 FILE MEDLINE
L7         236 FILE CAPLUS
'CACHEXIA' NOT IN RELATIONSHIP FILE
RELATIONSHIP CODE 'ALL' IGNORED
'URINE' NOT IN RELATIONSHIP FILE
RELATIONSHIP CODE 'ALL' IGNORED
L8          54 FILE BIOSIS
L9        6800 FILE EMBASE
RELATIONSHIP 'ALL' IGNORED
RELATIONSHIPS DO NOT EXIST FOR FIELD 'CT'
RELATIONSHIP 'ALL' IGNORED
RELATIONSHIPS DO NOT EXIST FOR FIELD 'CT'
L10         30 FILE WPIDS
'CACHEXIA' NOT IN RELATIONSHIP FILE
RELATIONSHIP CODE 'ALL' IGNORED
LEFT TRUNCATION IGNORED FOR '?URIA?' FOR FILE 'JICST-EPLUS'
L11          4 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L12       7200 (L1 OR CACHEXIA OR CANCER OR TUMOUR OR TUMOR OR L2 OR
NEOPLASM?)
                AND (L3 OR URINE OR ?URIA?) AND (IMMUNE(W)(RESPONSE OR
STIMULAT
               ?) OR BACTERIA CELL WALL EXTRACT OR HEAT SHOCK PROTEIN)
Left truncation is not valid in the specified search field in the
specified file.  The term has been searched without left truncation.
Examples: '?TERPEN?' would be searched as 'TERPEN?' and '?FLAVONOID'
would be searched as 'FLAVONOID.'

If you are searching in a field that uses implied proximity, and you
used a truncation symbol after a punctuation mark, the system may
interpret the truncation symbol as being at the beginning of a term.
Implied proximity is used in search fields indexed as single words,
for example, the Basic Index.

=> s l12 and (apc or antigen present? cell! or dendrit? cell!)
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L13           2 FILE MEDLINE
L14          24 FILE CAPLUS
L15           0 FILE BIOSIS
L16         637 FILE EMBASE
L17           2 FILE WPIDS
L18           0 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L19         665 L12 AND (APC OR ANTIGEN PRESENT? CELL! OR DENDRIT? CELL!)

=> s l19 and (treat? or therap?) and (mammal? or human)
L20           0 FILE MEDLINE
L21          13 FILE CAPLUS
L22           0 FILE BIOSIS
L23         190 FILE EMBASE
L24           2 FILE WPIDS
L25           0 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L26         205 L19 AND (TREAT? OR THERAP?) AND (MAMMAL? OR HUMAN)

=> s l26 and isolat?
L27           0 FILE MEDLINE
L28           2 FILE CAPLUS
L29           0 FILE BIOSIS
L30          22 FILE EMBASE
L31           2 FILE WPIDS
L32           0 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L33          26 L26 AND ISOLAT?

=> dup rem l33
PROCESSING COMPLETED FOR L33
L34           26 DUP REM L33 (0 DUPLICATES REMOVED)

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L34  ANSWER 1 OF 26  EMBASE  COPYRIGHT 2001 ELSEVIER SCI. B.V.
2001252816  EMBASE  Research opportunities in transfusion medicine.
Silberstein
     L.E.; Toy P.. Dr. L.E. Silberstein, Jt. Program in Transfusion Medicine,
     Dana Farber Cancer Institute, Brigham and Women's Hospital, Bader 4, 300
     Longwood Ave, Boston, MA 02115, United States. Journal of the American
     Medical Association  285/5 (577-580)  7 Feb 2001.
     Refs: 29.
     ISSN: 0098-7484. CODEN: JAMAAP. Pub. Country: United States. Language:
     English. Summary Language: English.
AB   In recent years, the translation of basic research in transfusion
medicine
     has led to development of novel cellular therapies using
     well-characterized cell populations isolated from either bone
     marrow or blood (eg, hematopoietic stem and progenitor cells, T
     lymphocytes, dendritic cells). Refinements in cell
     therapies will make possible optimal stem cell engraftment, gene
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therapy, immunotherapy of **cancer** and infectious disease, and even solid organ regeneration. Moreover, the immune consequences of transfusion **therapy** are better appreciated and opportunities are at hand to prevent or blunt unwanted **immune responses**, such as platelet refractoriness and graft-vs-host disease. Transfusion medicine has become a broad, multidisciplinary field that has evolved beyond issues related to blood procurement and storage. The next series of advances in transfusion medicine will complement the current approaches of donor blood screening and viral/bacterial inactivation steps to ensure a safe and adequate blood supply.

L34 ANSWER 2 OF 26 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
2001188452 EMBASE **Dendritic cells** for specific **cancer** immunotherapy. Meidenbauer N.; Andreesen R.; Mackensen A.. A. Mackensen, Department of Hematology/Oncology, University of Regensburg, D-93042 Regensburg, Germany. Biological Chemistry 382/4 (507-520) 2001.
Refs: 161.
ISSN: 1431-6730. CODEN: BICHF3. Pub. Country: Germany. Language: English.
Summary Language: English.
AB The characterization of **tumor**-associated antigens recognized by **human** T lymphocytes in a major histocompatibility complex (MHC)-restricted fashion has opened new possibilities for immunotherapeutic approaches to the **treatment** of **human cancers**. **Dendritic cells** (DC) are professional **antigen presenting cells** that are well suited to activate T cells toward various antigens, such as **tumor** -associated antigens, due to their potent constimulatory activity. The availability of large numbers of DC, generated either from hematopoietic progenitor cells or monocytes in vitro or **isolated** from peripheral blood, has profoundly changed pre-clinical research as well as the clinical evaluation of these cells. Accordingly, appropriately pulsed or transfected DC may be used for vaccination in the field of infectious diseases or **tumor** immunotherapy to induce antigen-specific T cell responses. These observations led to pilot clinical trials of DC vaccination for patients with **cancer** in order to investigate the feasibility, safety, as well as the immunologic and clinical effects of this approach. Initial clinical studies of **human** DC vaccines are generating encouraging preliminary results demonstrating induction of **tumor**-specific **immune responses** and **tumor** regression. Nevertheless, much work is still needed to address several variables that are critical for optimizing this approach and to determine the role of DC-based vaccines in **tumor** immunotherapy.

L34 ANSWER 3 OF 26 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
2001136627 EMBASE Multiple co-stimulatory signals are required for triggering proliferation of T cells from **human** secondary lymphoid tissue. Agrawal S.G.; Marquet J.; Plumas J.; Rouard H.; Delfau-Larue M.-H.; Gaulard P.; Boumsell L.; Reyes F.; Bensussan A.; Farcet J.-P.. J.-P. Farcet, Laboratoire d'Immunologie Biologique, Hopital Henri Mondor, 94010

Creteil, France. International Immunology 13/4 (441-450) 2001.
Refs: 70.
ISSN: 0953-8178. CODEN: INIMEN. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB Vaccine-based **therapies** are being developed for a variety of **cancers** and their efficacy will be determined by their ability to stimulate T cells in the secondary lymphoid tissue. We found that T cells **isolated** from **human** secondary lymphoid organs (LT-T), in contrast to peripheral blood T cells (PB-T) are hyporesponsive to cross-linked anti-CD3 mAb (CD3c) even in the presence of exogenous IL-2. Using mAb to trigger CD2 and CD28 co-stimulatory molecules, we found that such dual co-stimulation of LT-T induces profound and sustained responses including CD25 expression, IL-2 secretion and proliferation. Different levels of co-stimulation produced a hierarchical pattern of responses in LT-T, which correlated with the degree of CD3-TCR down-regulation. Mature **antigen- presenting cells** (**APC**) restored the capacity of LT-T to proliferate to stimulation of the CD3-TCR complex. Blocking studies demonstrated that optimal proliferation was critically dependent on co-stimulation via CD2 and CD28 engaged by their ligands on the **APC**. therefore, LT-T have increased co-stimulatory requirements as compared to PB-T, i.e. multiple co-stimulatory signals coupled to CD3-TCR triggering. Furthermore, LT-T we found to be dependent on **APC** for survival, in contrast to PB-T. Clearly, LT-T don not behave in a comparable way to PB-T and in vitro experiments assessing novel **cancer** vaccines should therefore use LT-T as the most appropriate population of responder T cells.

L34 ANSWER 4 OF 26 CAPLUS COPYRIGHT 2001 ACS

2000:191191 Document No. 132:235901 Immune activation by double-stranded polynucleotides. Kohn, Leonard D.; Suzuki, Koichi; Mori, Atsumi; Iishi, Ken; Klinman, Dennis M.; Rice, John M. (USA). PCT Int. Appl. WO 2000015768 A1 20000323, 147 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US20782 19990910. PRIORITY: US 1998-151612 19980911.

AB Double-stranded polynucleotide activates the expression of immune recognition mols. The polynucleotide can have a minimal length and activates the expression of mols. not encoded by a nucleotide sequence that is not necessarily related to the polynucleotide. The present invention provides for a simple and specific system to activate expression of Class I and/or Class II mols. of the major histocompatibility complex (MHC), and allows regulation of expression of MHC mols. on the cell-surface of **antigen presenting cells** and other immune cells. Also provided are systems for the screening, identification, and **isolation** of compds. that increase or decrease this activation. The method is useful for immunotherapy or genetherapy of infections, **cancers** and autoimmune diseases.

L34 ANSWER 5 OF 26 CAPLUS COPYRIGHT 2001 ACS
2000:755262 Document No. 133:320983 Composition and method for modulating dendritic cell-T cell interaction. Figdor, Carl Gustav; Geijtenbeek, Teunis Bernard Herman; Van Kooyk, Yvette; Torensma, Ruurd (Koninklijke Universiteit Nijmegen, Neth.). Eur. Pat. Appl. EP 1046651 A1 20001025, 44
pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO. (English). CODEN: EPXXDW. APPLICATION: EP 1999-201204 19990419. PRIORITY: US 2000-PV176924 20000120.

AB The present invention relates to the use of a compd. that binds to a C-type lectin on the surface of a dendritic cell, in the prepn. of a compn. for modulating, in particular reducing, the **immune response** in an animal, in particular a **human** or another **mammal**. The compn. in particular modulates the interactions between a dendritic cell and a T-cell, more specifically between a C-type lectin on the surface of a dendritic cell and an ICAM receptor on the surface of a T-cell. The compns. can be used for preventing/inhibiting **immune responses** to specific antigens, for inducing tolerance, for immunotherapy, for immunosuppression, for the **treatment** of auto-immune diseases, the **treatment** of allergy, and/or for inhibiting HIV infection. The compd. that binds to a C-type lectin is preferably chosen from mannose, fucose, plant lectins, antibiotics, sugars, proteins or antibodies against C-type lectins. The invention also relates to such antibodies, and to a method for **isolating dendritic cells** using such antibodies.

L34 ANSWER 6 OF 26 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
2000404636 EMBASE Induction of antitumor immunity by vaccination of **dendritic cells** transfected with MUC1 RNA. Koido S.; Kashiwaba M.; Chen D.; Gendler S.; Kufe D.; Gong J.. Dr. J. Gong, Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA 02115, United States. Journal of Immunology 165/10 (5713-5719) 15 Nov 2000. Refs: 57.
ISSN: 0022-1767. CODEN: JOIMA3. Pub. Country: United States. Language: English. Summary Language: English.

AB **Dendritic cells** (DC) are potent **APCs**. In this study, murine bone marrow-derived DC were transfected with RNA encoding the MUC1 Ag that is aberrantly overexpressed in **human** breast and other carcinomas. The MUC1 RNA-transfected DC exhibited cell surface expression of MUC1 and costimulatory molecules. After injection at the base of the tail, the transfected DC were detectable in inguinal lymph nodes by dual immunochemical staining. Vaccination of wild-type mice with MUC1 RNA-transfected DC induced anti-MUC1 **immune responses** against MUC1-positive MC38/MUC1, but not MUC1-negative, **tumor** cells. Mice immunized with the transfected DC were protected against challenge with MC38/MUC1 **tumor** cells. Furthermore, mice with established MC38/MUC1 **tumors** were eliminated after receiving the vaccination. CTLs **isolated** from mice immunized with the transfected DC exhibited specific cytolytic activity against MC38/MUC1 **tumor** cells. In contrast to these findings, there was

little if any anti-MUC1 immunity induced with the transfected DC in MUC1 transgenic (MUC1.Tg) mice. However, coadministration of the transfected DC
and IL-12 reversed the unresponsiveness to MUC1 Ag in MUC1.Tg mice and induced MUC1-specific **immune responses**. These findings demonstrate that vaccination of DC transfected with MUC1 RNA and IL-12 reverses tolerance to MUC1 and induces immunity against MUC1-positive **tumors**.

L34 ANSWER 7 OF 26 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
2000143371 EMBASE LIGHT, a TNF-like molecule, costimulates T cell proliferation and is required for dendritic cell-mediated allogeneic T cell response. Tamada K.; Shimozaki K.; Chapoval A.I.; Zhai Y.; Su J.; Chen S.-F.; Hsieh S.- L.; Nagata S.; Ni J.; Chen L.. Dr. L. Chen, Department of Immunology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, United States. chen.lieping@mayo.edu. Journal of Immunology 164/8 (4105-4110) 15 Apr 2000.
Refs: 37.
ISSN: 0022-1767. CODEN: JOIMA3. Pub. Country: United States. Language: English. Summary Language: English.
AB LIGHT is a recently identified member of the TNF superfamily and its receptors, herpesvirus entry mediator and lymphotoxin .beta. receptor, are
found in T cells and stromal cells. In this study, we demonstrate that LIGHT is selectively expressed on immature **dendritic cells** (DCs) generated from **human** PBMCs. In contrast, LIGHT is not detectable in DCs either freshly **isolated** from PBMCs or rendered mature in vitro by LPS **treatment**. Blockade of LIGHT by its soluble receptors, lymphotoxin .beta. receptor-Ig or HVEM-Ig,
inhibits the induction of DC-mediated primary allogeneic T cell response. Furthermore, engagement of LIGHT costimulates **human** T cell proliferation, amplifies the NF-.kappa.B signaling pathway, and preferentially induces the production of IFN- .gamma., but not IL-4, in the presence of an antigenic signal. Our results suggest that LIGHT is a costimulatory molecule involved in DC-mediated cellular **immune responses**.

L34 ANSWER 8 OF 26 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
2000087764 EMBASE Induction of **tumor** immunity and cytotoxic T lymphocyte responses using **dendritic cells** transfected with messenger RNA amplified from **tumor** cells. Boczkowski D.; Nair S.K.; Nam J.-H.; Lyerly H.K.; Gilboa E.. E. Gilboa, Department of Surgery, Box 2601, Duke University Medical Center, Durham, NC 27710, United States. e.gilboa@cgct.duke.edu. Cancer Research 60/4 (1028-1034) 15 Feb 2000.
Refs: 25.
ISSN: 0008-5472. CODEN: CNREA8. Pub. Country: United States. Language: English. Summary Language: English.
AB Unique patient-specific **tumor** antigens may constitute the dominant antigens in the antitumor **immune response**. Hence, vaccination with the patient's own repertoire of **tumor** antigens may offer a superior strategy to elicit protective immunity. We have shown previously that **dendritic cells** transfected with mRNA **isolated** from **tumor** cells stimulate potent

CTL responses and engender protective immunity in **tumor**-bearing mice. In the current study, we demonstrate that **tumor** mRNA, **isolated** from murine **tumor** cell lines or from primary **human tumor** cells microdissected from frozen tissue sections, can be amplified without loss of function. This study provides the foundations for an effective and broadly applicable **treatment** that does not require the characterization of the relevant antigenic profile in each patient and will not be limited by **tumor** tissue availability for antigen preparation.

L34 ANSWER 9 OF 26 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
2000242840 EMBASE Effects of cimetidine on the induction of **dendritic cells** derived from monocytes of an advanced colon **cancer** patient. Kubota T.; Fujiwara H.; Ueda Y.; Fuji N.; Ito T.; Yoshimura T.; Yamagishi H.. Dr. T. Kubota, Department of Digestive Surgery, Kyoto Prefect. Univ. of Medicine, 465 Kajii-cho, Kawaramachi Hirokoji, Kyoto 602-8566, Japan. Biotherapy 14/5 (551-553) 2000.
Refs: 3.
ISSN: 0914-2223. CODEN: BITPE. Pub. Country: Japan. Language: Japanese. Summary Language: English; Japanese.
AB It has been reported that cimetidine, a H2-receptor antagonist, can stimulate a host's anti-**tumor** cell-mediated immunity through the inhibition of suppressor T cells or the enhancement of NK/LAK activity. On the other hand, **dendritic cells** (DC) are known to be potent **antigen-presenting cells** capable of stimulating naive T cell **immune responses**, and are now actively utilized as DC vaccines by pulsing with **tumor** antigen-derived peptides for **cancer** immunotherapy. However, at present, little is known about the influence of cimetidine on the function of DC. In this study, we performed an in vitro investigation on the effects of cimetidine on the induction of monocyte-derived DC. Peripheral blood mononuclear cells (PBMC) were **isolated** from an advanced colon **cancer** patient by leukapheresis and monocytes were obtained following dish adherence for 2 hr. Then, they were cultured in the presence of GM-CSF, IL-4 and histamine with or without cimetidine. After 7 days of culture, they were assayed by flow cytometry for the surface expression of maturation markers of DC. It was shown that histamine inhibited the induction of DC from monocytes and cimetidine blocked the inhibitory effect of histamine in a dose-dependent manner. This effect was considered to be due to the inhibition by cimetidine of the binding of histamine to H2- receptor expressed on monocytes.

L34 ANSWER 10 OF 26 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
2000185268 EMBASE Immuno-gene **therapy** for **cancer**.
Kawakami Y.. Dr. Y. Kawakami, Division of Cellular Signaling, Inst. for Advanced Medical Research, Keio University School of Medicine, 35 Shinanomachi, Shinjuku, Tokyo 160-8582, Japan. Biotherapy 14/4 (345-350) 2000.
Refs: 10.
ISSN: 0914-2223. CODEN: BITPE. Pub. Country: Japan. Language: Japanese. Summary Language: English; Japanese.
AB A variety of molecules involved in the immune system have recently been **isolated**. These molecules have allowed the design of immunological

interventions of **immune responses** to **human cancer**, or so called immuno-gene **therapy**. Clinical trials have been performed in Europe and the U.S. using various protocols, including gene-modified T cells; highly immunogenic **cancer** cells transfected with genes encoding cytokines, co-stimulatory molecules, and foreign antigens; immunization with **tumor** antigen genes as forms of plasmids and recombinant viruses; and immunization with **dendritic cells** transduced with **tumor** antigen genes. However, the anti-**tumor** effects observed in these reports have been limited. Improvement of various points will be necessary to establish immuno-gene **therapy** for **cancer** on the basis of fundamental research on immunoregulation against **cancer**, including **isolation** of **tumor** antigens and analysis of **tumor** escape mechanisms.

L34 ANSWER 11 OF 26 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

2000246030 EMBASE In vitro generation of **dendritic cells** derived from cryopreserved CD34+ cells mobilized into peripheral blood in lymphoma patients. Enomoto M.; Nagayama H.; Sato K.; Xu Y.; Asano S.; Takahashi T.A.. T.A. Takahashi, Department of Cell Processing, Institute of Medical Science, University of Tokyo, 4-6-1 Shirokanedia, Minato-ku, Tokyo 108-8639, Japan. Cytotherapy 2/2 (95-104) 2000.
Refs: 21.
ISSN: 1465-3249. CODEN: CYTRF3. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB Background: **Dendritic cells** (DC) are **APC** that initiate primary T-cell dependent **immune responses**. They have been shown to be generated from CD34+ cells in BM, placental/umbilical cord blood (CB), and G-CSF mobilized peripheral blood CD34+ cells (PBSC). In recent clinical studies, DC were used as a vaccine for **cancer** patients and showed induction of their antitumor effects. Cryopreservation of CD34+ cells is important to extend the availability of cellular **therapy** with DC. However, little is known about the effect of cryopreservation on the functional maturation of DC. Methods: PBSC harvested from lymphoma patients mobilized with G-CSF and undergoing leukapheresis were cryopreserved at -135 .degree.C for 3 days. Freshly **isolated** or cryopreserved PBSC were cultured with GM-CSF/SCF/**tumor** necrosis factor-.alpha. (TNF-.alpha.). After 14 days of culture, DC were harvested, washed, and used for phenotypical and functional analysis. Results: Cryopreserved PBSC, as well as freshly-**isolated** PBSC cultured for 14 days, gave rise to CD1a+/CD4+/CD11c+/CD14low+/CD25-/C D40+/CD45RO+/CD80+/CD83+/CD86+/HLA-DR+ cells with dendritic morphology. DC derived from cryopreserved PBSC mobilized with G-CSF showed a similar endocytic capacity and chemotactic migratory capacities when compared with DC derived from freshly-**isolated** G-CSF mobilized PBSC. These DC also exhibited similar capacities in the primary allogeneic T-cell response. Discussion: These results indicate that cryopreserved G-CSF mobilized PBSC cultured with GM-CSF/SCF/TNF-.alpha. gave rise to DC that were morphologically, phenotypically and functionally similar to DC derived from fresh G-CSF mobilized PBSC. The observation indicates the clinical usefulness of cryopreserved CD34+ cells from lymphoma patients.

L34 ANSWER 12 OF 26 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
2000141467 EMBASE **Immune response** induced by **dendritic cells** induce apoptosis and inhibit proliferation of **tumor** cells. Li M.S.; Yuan A.L.; Zhang W.D.; Chen X.Q.; Tian X.H.; Piao Y.J.. M.S. Li, Department of Gastroenterology, Nanfang Hospital, First Military Medical University, Guangzhou 510515, Guangdong Province, China. World Chinese Journal of Digestology 8/1 (56-58) 2000.
Refs: 5.
ISSN: 1009-3079. CODEN: SHXZF2. Pub. Country: China. Language: Chinese. Summary Language: English.
AB AIM: To study if the **immune response** in viva induced by **dendritic cells** (DC) pulsed with **tumor** extract can inhibit the growth of implanted **tumor** in nude rats. METHODS: DC **isolated** and purified was from hepatocellular **cancer** (HCC) patients with combination of granulocyte/ macrophage colony stimulating factor and interleukin 4; **tumor** associated antigen (TAA) extracted from HCC call line HepG2 **tumor** calls; T lymphocyte initiated with DC pulsed by the TAA to cytotoxic T lymphocyte (CTL); CTL implanted to inhibit the growth of implanted **tumor** in rats; and the apoptosis and proliferation of **tumor** calls were evaluated. RESULTS: CTL induced by DC pulsed with TAA can inhibit the growth of implanted **tumor** in rats by inducing apoptosis and inhibiting proliferation of **tumor** cells. CONCLUSION: DC pulsed by TAA may play an important role in the **treatment** of **tumors**.

L34 ANSWER 13 OF 26 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2000-116291 [10] WPIDS
AB WO 9958978 A UPAB: 20000228
NOVELTY - The **immune response** of a **mammal** to circulating **tumor** marker proteins (I), or to cells that express (I), is detected by:
(i) **treating** a body fluid sample with a panel of two or more distinct **tumor** marker antigens (Ag); and
(ii) detecting presence or absence of complexes between Ag and specific autoantibodies (AAb).
Presence of the complex indicates an **immune response**.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(a) assay kit containing a panel of at least two Ag and system for contacting this with sample;
(b) similar method in which the amount of each complex formed is determined to identify which Ag elicits the strongest response;
(c) preparation comprising a **human** MUC1 protein having all the antigenic characteristics of a MUC1 protein obtained from the body fluids of a patient with advanced breast **cancer**;
(d) (I) that is substantially equivalent to MUC1, is **isolated** from serum of a patient with advanced breast **cancer** and has affinity for antibody 115D8 3-6 times greater than MUC1 **isolated** from normal **human urine**;
(e) detecting or determining AAb specific for MUC1 using the antigen of (c) or (d);
(f) quantifying the **immune response** to (I) by

measuring the amount of complex formed with AAb;
(g) assay kit for method (f);
(h) determining if vaccination with a MUC1-containing preparation has been successful by **treating** serum from the subject with the antigen of (c) or (d), with formation of a complex indicating success; and
(i) detecting recurrent disease in a patient who has been **treated** for **cancer** by detecting complex formation between MUC1 and specific AAb.
ACTIVITY - None given.
MECHANISM OF ACTION - None given.
USE - The method is used:
(i) to diagnose **cancer**, particularly breast, bladder, colorectal, prostatic or ovarian, including recurrence of disease;
(ii) to identify subjects at risk of developing **cancer**;
(iii) to establish a (I) profile, e.g. for monitoring disease;
(iv) to predict and measure response to **treatment** (hormone, chemo, radio, anti-growth factor **therapies**, immunotherapy or vaccination);
(v) for selecting a vaccine (i.e. identifying Ag that elicits the greatest response); and
(vi) to identify a successful vaccination with a MUC1 preparation.
ADVANTAGE - The method can detect early neoplastic or carcinogenic changes in asymptomatic subjects. Using a panel of Ag, rather than a single Ag, provides a more accurate assay that is more generally useful (greater sensitivity and fewer false negatives, also less subjective than mammography or ultrasonic examinations). The procedure is not invasive and can be repeated as required.
Dwg.0/15

L34 ANSWER 14 OF 26 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1999-430163 [36] WPIDS
CR 1998-216926 [19]
AB WO 9932634 A UPAB: 20010801
NOVELTY - Heat-killed Mycobacterium vaccae, or recombinant M. vaccae proteins, may be employed to activate T cells and natural killer (NK) cells, to stimulate the production of cytokines, to enhance the expression of co-stimulatory molecules on **dendritic cells** and monocytes, and to enhance dendritic cell maturation and function.
DETAILED DESCRIPTION - A polypeptide (I) comprising an immunogenic portion of an **isolated** M. vaccae antigen is new, and is selected from the 91, 136, 228, 231, 748, 221, 161, 541, 327, 134, 108, 348,471, 722, 297, 670, 152, 331, 69, 268, 41, 111, 370, 159, 285, 243, 223, 187, 340 or 173 amino acid sequence given in the specification. Alternatively, (I) is at least 50%, 75% or 95% identical to one of these sequences, as measured by computer algorithm BLASTP. (I) is encoded by a polynucleotide (II), selected from the 273, 554, 808, 683, 1125, 666, 480, 1626, 985, 403, 336, 1111, 1420, 2172, 898, 2013, 520, 1071, 207, 898, 337, 1164, 650, 743 or 858 base pair sequence given in the specification. Alternatively, (II) is the complement of one of these sequences, or has a 99% probability of being the same sequence as measured by computer algorithm BLASTN.

INDEPENDENT CLAIMS are also included for the following:

(1) an expression vector comprising (II);

(2) a host cell, preferably E. coli, mycobacteria, insect, yeast or **mammalian** cells, transformed with the vector of (1);

(3) a fusion protein comprising (I);

(4) a pharmaceutical composition comprising (I) or (II) or the fusion protein of (3) and a physiologically acceptable carrier;

(5) a vaccine comprising (I) or (II) or the fusion protein of (3) and a non-specific **immune response** amplifier;

(6) a method for enhancing an **immune response** in a patient, comprising administering the pharmaceutical composition of (4) or the vaccine of (5);

(7) a method for the **treatment** of a disorder in a patient, comprising administering the pharmaceutical composition of (4) or the vaccine of (5);

(8) a method for the **treatment** of a disorder in a patient, comprising administering a composition comprising a component selected from:

(a) inactivated M. vaccae cells;

(b) delipidated and deglycolipidated M. vaccae cells depleted of mycolic acids;

(c) delipidated and deglycolipidated M. vaccae cells depleted of mycolic acid and arabinogalactan; and

M. vaccae culture filtrate;

(9) a method for enhancing a non-specific **immune response** to an antigen, comprising administering a polypeptide comprising an immunogenic portion of a M. vaccae antigen selected from:

(a) the 376 or 223 amino acid sequence given in the specification; or

(b) sequences at least 80% identical to these, as measured by computer algorithm BLASTP;

(10) a method for detecting mycobacterial infection in a patient, comprising contacting the dermal cells of the patient with (I) and detecting an **immune response**, e.g. induration, on the patients skin;

(11) a diagnostic kit comprising (I) and apparatus sufficient to contact the polypeptide with the dermal cells of a patient;

(12) a method for detecting mycobacterial infection in a biological sample, comprising contacting the sample with (I) and detecting the presence of antibodies that bind to the polypeptide. The polypeptides are optionally bound to a solid support;

(13) a method for detecting mycobacterial infection in a biological sample, comprising contacting the sample with a binding agent, e.g. a mono- or a polyclonal antibody, which is capable of binding to (I) and detecting this binding;

(14) a diagnostic kit comprising (I) (preferably immobilized on a solid support) and a detection reagent, e.g. a reporter group (which is especially a radioisotope, a fluorescent group, a luminescent group, an enzyme, biotin or dye particles) conjugated to a binding agent (which is especially an anti-immunoglobulin, Protein G, Protein A or lectin);

(15) a mono- or polyclonal antibody that binds to (I); and

(16) a method for enhancing a non-specific **immune response** to an antigen, comprising administering a composition

comprising a component selected from:

(a) delipidated and deglycolipidated M. vaccae cells depleted of mycolic acids;

(b) delipidated and deglycolipidated M. vaccae cells depleted of mycolic acid and arabinogalactan.

ACTIVITY - Antiasthmatic; Antiinflammatory; Antipsoriatic; Cytostatic; Dermatological; Tuberculostatic.

MECHANISM OF ACTION - Vaccine.

USE - The compositions can be used for the treatment, prevention, and detection of disorders including infectious diseases (claimed), immune disorders (claimed) and cancer. In particular, the compounds and methods are used for treatment of diseases of the respiratory system (claimed), such as mycobacterial infections (claimed), asthma (claimed), allergies, tuberculosis, leprosy, sarcoidosis and lung cancers, and disorders of the skin (claimed) such as psoriasis (claimed), atopic dermatitis, eczema, allergic contact dermatitis, alopecia areata, and skin cancers such as basal carcinoma, squamous cell carcinoma and melanoma.

The products can also be used as vaccines or in immunotherapy.

ADVANTAGE - Of all the available therapies for treating cutaneous lesions, only interferon possesses a specific antiviral mode of action, by reproducing the body's immune response to infection. However, Interferon treatment cannot eradicate viruses. Interferon treatment is also associated with systemic adverse effects, and requires multiple injections, at a significant economic cost. Use of M. vaccae to immunize individuals overcomes these problems.

Dwg.0/13

L34 ANSWER 15 OF 26 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

1999278985 EMBASE CpG DNA: A potent signal for growth, activation, and maturation of **human dendritic cells**.

Hartmann G.; Weiner G.J.; Krieg A.M.. A.M. Krieg, Department of Internal Medicine, University of Iowa, 540 EMRB, Iowa City, IA 52242, United States. amkrieg@blue.weeg.uiowa.edu. Proceedings of the National Academy of Sciences of the United States of America 96/16 (9305-9310) 6 Aug 1999.

Refs: 48.

ISSN: 0027-8424. CODEN: PNASA6. Pub. Country: United States. Language: English. Summary Language: English.

AB DNA molecules containing unmethylated CpG-dinucleotides in particular base contexts ('CpG motifs') are excellent adjuvants in rodents, but their effects on **human** cells have been less clear. **Dendritic cells** (DCs) form the link between the innate and the acquired immune system and may influence the balance between T helper 1 (Th1) and Th2 **immune responses**. We evaluated the effects of CpG oligodeoxynucleotides alone or in combination with granulocyte-macrophage colony-stimulating factor (GMCSF) on different classes of purified **human** DCs. For primary dendritic precursor cells **isolated** from **human** blood, CpG oligonucleotides alone were superior to GMCSF in promoting survival and maturation (CD83 expression) as well as expression of class II MHC and the costimulatory molecules CD40, CD54, and CD86 of DCs. Both CD4- positive and CD4-negative peripheral blood

dendritic precursor cells responded to CpG DNA which synergized with GMCSF
but these DCs showed little response to lipopolysaccharide (LPS). In contrast, monocyte-derived DCs did not respond to CpG, but they were highly sensitive to LPS, suggesting an inverse correlation between CpG and
LPS sensitivity in different subsets of DCs. Compared with GMCSF, CpG-**treated** peripheral blood DCs showed enhanced functional activity in the mixed lymphocyte reaction and induced T cells to secrete increased levels of Th1 cytokines. These findings demonstrate the ability of specific CpG motifs to strongly activate certain subsets of **human** DCs to promote Th1-like **immune responses**, and support the use of CpG DNA- based trials for immunotherapy against **cancer**, allergy, and infectious diseases.

L34 ANSWER 16 OF 26 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
1999334897 EMBASE Hyperexpression of CD40 ligand (CD154) in inflammatory bowel disease and its contribution to pathogenic cytokine production. Liu Z.; Colpaert S.; D'Haens G.R.; Kasran A.; De Boer M.; Rutgeerts P.; Geboes
K.; Ceuppens J.L.. Dr. J.L. Ceuppens, Lab. of Experimental Immunology, U.Z. Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium. Jan.Ceuppens@med.kuleuven.ac.be. Journal of Immunology 163/7 (4049-4057) 1 Oct 1999.
Refs: 58.
ISSN: 0022-1767. CODEN: JOIMA3. Pub. Country: United States. Language: English. Summary Language: English.
AB CD40 ligand (CD40L or CD154), a type II membrane protein with homology to TNF, is transiently expressed on activated T cells and known to be important for B cell Ig production and for activation and differentiation of monocytes and **dendritic cells**. Both Crohn's disease and ulcerative colitis are characterized by local production of cytokines such as TNF and by an influx of activated lymphocytes into inflamed mucosa. Herein, we investigated whether CD40L signaling participates in **immune responses** in these diseases. Our results demonstrated that CD40L was expressed on freshly **isolated** lamina propria T cells from these patients and was functional to induce IL-12 and
TNF production by normal monocytes, especially after IFN-.gamma. priming. The inclusion of a blocking mAb to CD40L or CD40 in such cocultures significantly decreased monocyte IL-12 and TNF production. Moreover, lamina propria and peripheral blood T cells from these patients, after in vitro activation with anti-CD3, showed increased and prolonged expression of CD40L as compared with controls. Immunohistochemical analyses indicated
that the number of CD40+ and CD40L+ cells was significantly increased in inflamed mucosa, being B cells/macrophages and CD4+ T cells, respectively.
These findings suggest that CD40L up-regulation is involved in pathogenic cytokine production in inflammatory bowel disease and that blockade of CD40-CD40L interactions may have **therapeutic** effects for these patients.

L34 ANSWER 17 OF 26 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
1999143761 EMBASE Identification of MAGE-3 epitopes presented by HLA-DR

molecules to CD4+ T lymphocytes. Chaux P.; Vantomme V.; Stroobant V.; Thielemans K.; Corthals J.; Luiten R.; Eggermont A.M.M.; Boon T.; Van der Bruggen P.. P. Van der Bruggen, Ludwig Institute for Cancer Research, UCL 74.59, Avenue Hippocrate 74, B-1200 Brussels, Belgium. vanderbruggen@licr.ucl.ac.be. Journal of Experimental Medicine 189/5 (767-777) 1 Mar 1999.
Refs: 52.
ISSN: 0022-1007. CODEN: JEMEAV. Pub. Country: United States. Language: English. Summary Language: English.

AB MAGE-type genes are expressed by many **tumors** of different histological types and not by normal cells, except for male germline cells, which do not express major histocompatibility complex (MHC) molecules. Therefore, the antigens encoded by MAGE-type genes are strictly **tumor** specific and common to many **tumors**. We describe here the identification of the first MAGE-encoded epitopes presented by histocompatibility leukocyte antigen (HLA) class II molecules to CD4+ T lymphocytes. Monocyte-derived **dendritic cells** were loaded with a MAGE-3 recombinant protein and used to stimulate autologous CD4+ T cells. We **isolated** CD4+ T cell clones that recognized two different MAGE-3 epitopes, MAGE-3(114-127) and MAGE-3(121-134), both presented by the HLA-DR13 molecule, which is expressed in 20% of Caucasians. The second epitope is also encoded by MAGE-1, -2, and -6. Our procedure should be applicable to other proteins for the identification of new **tumor**-specific antigens presented by HLA class II molecules. The knowledge of such antigens will be useful for evaluation of the **immune response** of **cancer** patients immunized with proteins or with recombinant viruses carrying entire genes coding for **tumor** antigens. The use of antigenic peptides presented by class II in addition to peptides presented by class I may also improve the efficacy of **therapeutic** antitumor vaccination.

L34 ANSWER 18 OF 26 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
1999090828 EMBASE Dendritic cell vaccines for **cancer** immunotherapy.
Timmerman J.M.; Levy R.. J.M. Timmerman, Department of Medicine, Division of Oncology, Stanford University School Medicine, Stanford, CA 94305, United States. jtimmer@leland.stanford.edu. Annual Review of Medicine 50/- (507-529) 1999.
Refs: 111.
ISSN: 0066-4219. CODEN: ARMCAH. Pub. Country: United States. Language: English. Summary Language: English.

AB **Human tumors** express a number of protein antigens that can be recognized by T cells, thus providing potential targets for **cancer** immunotherapy. **Dendritic cells** (DCs) are rare leukocytes that are uniquely potent in their ability to present antigens to T cells, and this property has prompted their recent application to **therapeutic cancer** vaccines. **Isolated** DCs loaded with **tumor** antigen ex vivo and administered as a cellular vaccine have been found to induce protective and **therapeutic** anti-**tumor** immunity in experimental animals. In pilot clinical trials of DC vaccination for patients with non-Hodgkin's lymphoma and melanoma, induction of anti-**tumor immune responses** and **tumor** regressions have

been observed. Additional trials of DC vaccination for a variety of **human cancers** are under way, and methods for targeting **tumor** antigens to DCs in vivo are also being explored. Exploitation of the antigen-presenting properties of DCs thus offers promise for the development of effective **cancer** immunotherapies.

L34 ANSWER 19 OF 26 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
2000145903 EMBASE Presentation of **tumor** antigens. The role of **dendritic cells**. Paglia P.; Colombo M.P.. P. Paglia, Immunotherapy and Gene Tnerapy Unit, Istituto Nazionale Tumori, Via Venezian i, 20133 Milano, Italy. Minerva Biotecnologica 11/4 (261-270) 1999.
Refs: 68.
ISSN: 1120-4826. CODEN: MIBIFK. Pub. Country: Italy. Language: English. Summary Language: English.
AB **Human tumors** express a number of protein antigens that can be recognized by T cells, thus providing potential targets for **cancer** immunotherapy. **Dendritic cells** are rare leukocytes that are uniquely potent in their ability to present antigens to T cells, and this property has prompted their recent application to **therapeutic cancer** vaccines. **Isolated dendritic cells** loaded with **tumor** antigen ex vivo and administered as a cellular vaccine have been found to induce protective and **therapeutic** antitumor immunity in experimental animals. In pilot clinical trials of **dendritic cells** vaccination for patients with non-Hodgkints lymphoma and melanoma, induction of anti-**tumor immune responses** and **tumor** regressions have been observed. Additional trials of **dendritic cells** vaccination for a variety of **human cancers** are underway, and methods for targeting **tumor** antigens to **dendritic cells** in vivo are also being explored. Exploitation of the antigen-presenting properties of **dendritic cells** thus offers promise for the development of effective **cancer** immunotherapies.

L34 ANSWER 20 OF 26 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
1999153403 EMBASE Generation of **dendritic cells** from patients with chronic myelogenous leukemia. Heinzinger M.; Waller C.F.; Von den Berg A.; Rosenstiel A.; Lange W.. W. Lange, Department of Hematology-Oncology, University Medical Center Freiburg, Hugstetter Strasse 55, D-79106 Freiburg, Germany. Annals of Hematology 78/4 (181-186) 1999.
Refs: 24.
ISSN: 0939-5555. CODEN: ANHEE8. Pub. Country: Germany. Language: English. Summary Language: English.
AB **Dendritic cells** (DCs) are professional **antigen -presenting cells** (**APCs**) specialized to internalize, process, and present antigen. They have the capacity to stimulate the primary **immune response** of resting T-cells. We generated DCs from the adherent cell fraction of peripheral blood. as well as from purified CD34+ cells from CML patients. Characterizing DCs from ten CML patients by flow cytometry, we found that these cells are highly positive for HLA-DR, CD1a, CD23, and CD80 and negative for CD14, CD15, and CD16. The yield of DCs ranged from 19.5 to 68%. In addition, we used a functional test of FITC-dextran uptake to

verify that early DCs take up large particles (0.5-3 .mu.m) by macropinocytosis while monocytes do not. FITC-dextran uptake was detected by now cytometry, showing that DCs had accumulated these fluorescent particles. Electron-microscopic analysis showed no major morphological differences between normal and CML derived DCs. Furthermore, cultured DCs were **isolated** by FAC sorting for CD1a and HLA-DR expression. In these highly purified cells the Ph chromosome was detected by interphase fluorescence in situ hybridization (FISH) and by fluorescence immunophenotyping and interphase cytogenetics as a tool for the investigation of **neoplasms** (FICTION); 30-85% of DCs generated were Ph-chromosome positive. It might therefore be possible not only to prime T-cells with bcr/abl-specific synthetic peptides, but also to stimulate T cells directly with Ph-positive DCs. Use of DCs might serve as
a novel **therapeutic** approach in CML patients, due to their ability to induce highly specific T-cell responses in an autologous system.

L34 ANSWER 21 OF 26 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
1999279830 EMBASE Developing dendritic cell polynucleotide vaccination for prostate **cancer** immunotherapy. Berlyn K.A.; Ponniah S.; Stass S.A.; Malone J.G.; Hamlin-Green G.; Lim J.K.; Cottler-Fox M.; Tricot G.; Alexander R.B.; Mann D.L.; Malone R.W.. R.W. Malone, University of Maryland, School of Medicine, 10 South Pine Street, Baltimore, MD 21201-1192, United States. tmalo001@umaryland.edu. Journal of Biotechnology 73/2-3 (155-179) 1999.
Refs: 78.
ISSN: 0168-1656. CODEN: JBITD4.
Publisher Ident.: S 0168-1656(99)00118-2. Pub. Country: Netherlands.
Language: English. Summary Language: English.
AB Immunotherapy has been successfully used to **treat** some **human** malignancies, principally melanoma and renal cell carcinoma. Genetic-based **cancer** immunotherapies were proposed which prime T lymphocyte recognition of unique neo-antigens arising from specific mutations. Genetic immunization (polynucleotide vaccination, DNA vaccines)
is a process whereby gene **therapy** methods are used to create vaccines and immunotherapies. Recent findings indicate that genetic immunization works indirectly via a bone marrow derived cell, probably a type of dendritic antigen presenting cell (**APC**). Direct targeting of genetic vaccines to these cells may provide an efficient method for stimulating cellular and humoral **immune responses** to infectious agents and **tumor** antigens.
Initial studies have provided monocytic-derived dendritic cell (DC) **isolation** and culture techniques, simple methods for delivering genes into these cells, and have also uncovered potential obstacles to effective **cancer** immunotherapy which may restrict the utility of this paradigm to a subset of patients. Copyright (C) 1999 Elsevier Science
B.V.

L34 ANSWER 22 OF 26 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
97152228 EMBASE Document No.: 1997152228. Generation of effective **cancer** vaccines genetically engineered to secrete cytokines using adenovirus-enhanced transferrinfection (AVET). Schmidt W.; Maass G.;

Buschle M.; Schweighoffer T.; Berger M.; Herbst E.; Schilcher F.; Birnstiel M.L.. W. Schmidt, Research Inst. Molecular Pathology, Dr Bohr-Gasse 7, A-1030 Vienna, Austria. schmidt@aimp.una.ac.at. Gene 190/1 (211-216) 1997.
Refs: 10.
ISSN: 0378-1119. CODEN: GENED6.
Publisher Ident.: S 0378-1119(96)00537-9. Pub. Country: Netherlands. Language: English. Summary Language: English.

AB **Cancer** vaccines are based on the concept that **tumors** express novel antigens and thus differ from their normal tissue counterparts. Such putative **tumor**-specific antigens should be recognizable by the immune system. However, malignant cells are of self origin and only poorly immunogenic, which limits their capability to induce an anticancer **immune response**. To overcome this problem, **tumor** cells have been **isolated**, genetically engineered to secrete cytokine gene products and administered as **cancer** vaccines. We used adenovirus-enhanced transferrinfection (AVET), which allows high-level transient transgene expression, to introduce cytokine gene expression vectors into murine melanoma cells. The efficiency of AVET makes laborious selection and cloning procedures obsolete. We administered such modified **tumor** cells as **cancer** vaccines to syngeneic animals and investigated their impact on the induction of anticancer immunity. We found that IL-2 or GM-CSF gene-transfected murine melanoma cells are highly effective vaccines. Both of these cytokine-secreting vaccines cured 80% of animals which bore a subcutaneous micrometastasis prior to **treatment**, and induced potent antitumor immunity. The generation of antitumor immunity by these cytokine-secreting vaccines requires three different steps: (1) **tumor** antigen uptake and processing by **antigen-presenting cells** (**APCs**) at the site of vaccination; (2) migration of these **APCs** into the regional lymph nodes where T-cell priming occurs; (3) recirculation of specific, activated T-cells that recognize distinct **tumor** load and initiate its elimination. Extending our previously reported studies, we have now comprehensively analysed the requirements for effective antitumor vaccination in animals. This may also become the basis for **treatment** of **human cancer** patients.

L34 ANSWER 23 OF 26 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
96026999 EMBASE Document No.: 1996026999. .alpha.-Galactosyl (Gal.alpha.1-3Ga.beta.1-4GlcNAc-R) epitopes on **human** cells: Synthesis of the epitope on **human** red cells by recombinant primate .alpha.1,3-galactosyltransferase expressed in E. coli. Galili U.; Anaraki F.. Dept. of Microbiology/Immunology, Medical College of Pennsylvania, 2900 Queen Lane,Philadelphia, PA 19129, United States. Glycobiology 5/8 (775-782) 1995.
ISSN: 0959-6658. CODEN: GLYCE3. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB Developing methods for in vitro synthesis of the carbohydrate structure Gal.alpha.1-3Gal.beta.1-4GlcNAc-R (termed the a galactosyl epitope) on **human tumour** cells may be of potential clinical significance in **cancer** immunotherapy. **Tumour** vaccines

with this epitope would be opsonized in vivo by the natural anti-Gal antibody, which is present in large amounts in **humans**, and which interacts specifically with a-galactosyl epitopes. Binding of anti-Gal to .alpha.-galactosyl epitopes on **tumour** cell membranes is likely to increase uptake of the cell membranes by **antigen-presenting cells**, such as macrophages, via the adhesion of the Fc portion of anti-Gal to Fc receptors on these cells. This, in turn, may increase process;ng and presentation of **tumour** -associated antigens by **antigen-presenting cells**, and induce an effective **immune response** against **tumour** cells with these antigens. The present study describes a method for the synthesis of .alpha.-galactosyl epitopes on **human** cells (red cells used as a model) by recombinant .alpha.1,3galactosyltransferase (rec. .alpha.1,3GT) expressed in bacteria.

Escherichia coli was transformed with cDNA of the luminal portion of New World monkey rec. .alpha.1,3GT linked to six histidines (His)6 at the N-terminus. The enzyme produced by the bacteria was **isolated** from bacterial lysates on a nickel-Sepharose column and eluted with imidazole. This recombinant enzyme displayed acceptor specificity similar to that of rec. .alpha.1,3GT produced in COS cells. Red cells were pre-**treated** with sialidase for exposure of N-acetyllactosamine acceptors, then subjected to rec. .alpha.1,3GT activity. This enzyme synthesized at least 4 x 104 .alpha.-galactosyl epitopes/red cell. These epitopes were found to be accessible for binding of anti-Gal, as well as Bandeiraea simplicifolia IB4 lectin. It is argued that the method presented can be used for the synthesis of .alpha.-galactosyl epitopes on membranes of autologous **tumour** vaccines in **humans**.

L34 ANSWER 24 OF 26 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

93250270 EMBASE Document No.: 1993250270. The effect of aging on cytokine release and associated immunologic functions. Weigle W.O.. Department of Immunology IMM9, The Scripps Research Institute, 10666 North Torrey Pines Road,La Jolla, CA 92037, United States. Immunology and Allergy Clinics of North America 13/3 (551-569) 1993.

ISSN: 0889-8561. CODEN: INCAEP. Pub. Country: United States. Language: English. Summary Language: English.

AB An in vivo switch in T-cell subpopulations from those of naive to those of activated/memory subsets may offer some benefit to the aged by counteracting the overall deleterious effect of the aging process on the immune system. Although there is no question that **immune responses** are dampened by the aging process, the enhanced production of lymphokines by aged T cells in the presence of a decrease in proliferative responses to both mitogens and antigens (of the T-helper variety) is likely to be advantageous to the aged. The shift during the aging process from the naive subset to the activated/memory subset and the associated loss in the proliferative response of CD4+ T cells are accompanied by a decrease in intracellular calcium mobilization.51 It has been suggested that the primary cause of the dampening of immune function during the aging process is the inability of individual cells to undergo significant [Ca2+](i) mobilization. Because the aging process also is associated with a marked increase in secretion of lymphokines involved in

T helper cell function, however, it is questionable whether the loss of [Ca2+](i) mobilization in either CD4+ or CD8+ T cells is as detrimental to immune function as originally hypothesized. Differences in the function of CD44(hi) cells **isolated** from young adult and aged mice, although perhaps only quantitative, suggest that there must be some underlying difference in the events involved in either the activation or regulation of lymphokine production by these two groups. The enhanced production of lymphokines from CD4+ T-cell subsets from aged mice cannot be explained by their enhanced production of the regulatory lymphokine IL-10; if IL-10 down regulation was playing a major role, the production of lymphokines such as IFN.gamma. would be even more pronounced in the aged. A more effective use of a particular population of **APCs** by the aged T cell could result in enhanced lymphokine signals in the absence of additional T-cell expansion. The loss of MHC restriction58 during the aging process or the more effective use of activated B cells such as **APC** in aged mice also may account for increased lymphokine production. Additional expansion may not be required in these activated/memory cells, which already may have undergone maximum expansion. There are marked differences in the pathways of both T-cell activation and T-cell tolerance in Th1 (IL-2-producing) and Th2 (IL-4-producing) T-cell clone studies in vitro.22 It has been clearly established in mice, for example, that cloned CD4+ helper cells of the Th2 type are characterized by a T helper pattern of lymphokine secretion and do not mobilize intracellular calcium.22 It is likely that different types of T cells exist in vivo as well as in vitro, and that one of these subpopulations is of the activated/memory type (CD44(hi), IL-4-producing).

If that interpretation of the available data is correct, then the aged animal is adequately equipped with memory CD4+ and CD8+ T cells that can be activated to release lymphokines required to drive T helper cell activity, but is likely to be deficient in precursor T cells directed against new antigens that were not encountered during early life. Such new antigens could be associated with new strains of influenza virus or a malignant **neoplasm** of recent onset. It appears likely that, as a result of repeated expansion of T cells to environmental antigens throughout life, there is an accumulation of memory cells to these antigens with adequate lymphokine potential and a concomitant loss of naive cells. This scenario, applicable in the normal aging process, may be influenced directly by other events during the aging process. Exposure to infections, **tumors**, or various drugs may cause further down-regulation of the immune system in the aged patient. Future studies of cytokine synthesis and release should provide deeper insights into these, as well as other, immunologic changes noted during aging. Those insights may well lead to new **therapeutic** approaches, including cytokine **therapy** or administration of cytokine inhibitors or antagonists for **treatment** of immunologic problems in the elderly.

L34 ANSWER 25 OF 26 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
93159734 EMBASE Document No.: 1993159734. Clonal analysis of in vivo activated CD8+ cytotoxic T lymphocytes from a melanoma patient responsive to active specific immunotherapy. Kan-Mitchell J.; Qing Huang X.; Steinman L.; Oksenberg J.R.; Harel W.; Parker J.W.; Goedegebuure P.S.; Darrow T.L.; Mitchell M.S.. University of Southern California, School of Medicine, 2025 Zonal Avenue,Los Angeles, CA 90033, United States. Cancer Immunology Immunotherapy 37/1 (15-25) 1993.
ISSN: 0340-7004. CODEN: CIIMDN. Pub. Country: Germany. Language: English. Summary Language: English.

AB To study in vivo activated cytolytic T cells, CD8+ T cells clones were **isolated** from a melanoma patient (HLA A2, A11) **treated** with activity specific immunotherapy for 5 years. CD8+ T lymphocytes, purified by fluorescence-activated cell sorting, were cloned directly from the peripheral blood without **antigen-presenting cells** in the presence of irradiated autologous melanoma cells and recombinant interleukin-2 (IL-2) and IL-4. These conditions were inhibitory to de novo in vitro immunization. Of the 28 cytolytic CD8+ T cell clones, 21 lysed the autologous melanoma cell line (M7) but not the autologous lymphoblastoid cell line (LCL-7) nor the two melanoma cell lines, M1 (HLA A28) and M2 (HLA A28, A31), used to immunize the patient. The remaining 7 clones were also melanoma-specific, although their reactivities were broader, lysing several melanoma cell lines but not HLA-matched lymphoblastoid cells. Eight clones from the first group, ostensibly self-MHC-restricted, were expanded for further analysis. All expressed cluster determinants characteristic of mature, activated T cells, but not those of thymocytes, naive T cells, B cells or natural killer (NK) cells. They also expressed CD13, a myeloid marker. Of the 8 clones, 3 expressed both CD4 and CD8, but dual expression was not correlated with specificity of lysis. Two CD8+ and 2 CD4+ CD8+ clones were specific for the autologous melanoma cells, the other 4 were also reactive against other HLA-A2-positive melanomas. Cytotoxicity for both singly and doubly positive clones was restricted by HLA class I but not class II antigens. Analysis of the RNA expression of the T cell receptor (TCR) V.alpha. and V.beta. gene segments revealed heterogeneous usage by the A2-restricted clones and, perhaps, also by the broadly melanoma-specific clones. Apparent TCR-restricted usage was noted for the self-MHC-restricted clones; 2 of the 4 expressed the V.alpha.17/V.beta.7 dimer. Since the T cell clones were derived from separate precursors of circulating cytotoxic T lymphocytes (CTL), the V.alpha.17/V.beta.7 TCR was well represented in the peripheral blood lymphocytes of this patient. In summary, we show that melanoma cells presented their own antigens to stimulate the proliferation of melanoma-reactive CD8+ CTL. CTL with a rnage of melanoma specificities and different TCR .alpha..beta. dimers were encountered in this patient, perhaps as a result of hyperimmunization. Restricted TCR gene usage was noted only for classical self-MHC-restricted CD8+ T cell clones, although lysis of the autologous melanoma cells was effected by a variety of TCR structures. Molecular

definition of the TCR repertoire of well-characterized T cell clones in this and other patients should provide new insight into the **human** anti-**tumor immune response.**

L34 ANSWER 26 OF 26 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
92248783 EMBASE Document No.: 1992248783. An analysis of autologous T-cell anti-**tumour** responses in colon-carcinoma patients following active specific immunization (ASI). Patel B.T.; Lutz M.B.; Schlag P.; Schirrmacher V.. Department of Cellular Immunology, Institute of Immunology and Genetics, German Cancer Research Centre, Im Neuenheimer Feld 280,6900 Heidelberg, Germany. International Journal of Cancer 51/6 (878-885) 1992.
ISSN: 0020-7136. CODEN: IJCNAW. Pub. Country: United States. Language: English. Summary Language: English.
AB As part of a phase-II clinical trial of post-operative active specific immunization (ASI) with virus-modified autologous **tumour** cells (AuTu) in colorectal carcinoma patients, we have analyzed in vitro anti-AuTu **immune responses** with lymphocytes **isolated** from the peripheral blood (PBL) of 5 **treated** patients. The PBL of 3 'responder patients', those who developed a positive DTH reaction to AuTu, when stimulated in standard in vitro autologous lymphocyte **tumour**-cell cultures (ALTC), showed cytotoxic anti-AuTu reactivity only in association with natural-killer-cell(NK)-like activity. We removed nonspecific cytotoxic cells (CD56-positive) from PBL of colon carcinoma or melanoma patients and positively selected T cells with strong CD8 staining (CD8(hi)) using FACS. Following in vitro stimulation, specific cytotoxic T cells (CTL) directed against either autologous EBV-transformed B cells (AuEBV-B) or autologous melanoma cells were identified in the CD8(hi) T-cell population. However, even using this novel technique, no specific CTL against autologous colon carcinoma cell lines were detected in PBL from ASI-**treated** patients (2 DTH responders and 2 DTH non-responders). If AuTu-specific CTL precursors existed in these blood samples, their frequency must have been very low (less than 1 in 8 x 104 CD8 positive T cells). Sorted CD4 T cells from these patients, in the presence of autologous **antigen-presenting cells**, showed no specific anti-**tumour** proliferative response, and in one instance we observed inhibition of proliferation in the presence of **tumour** cells.

'IN' IS NOT A VALID FIELD CODE
L35 6 FILE MEDLINE
L36 10 FILE CAPLUS
L37 10 FILE BIOSIS
'IN' IS NOT A VALID FIELD CODE
L38 11 FILE EMBASE
L39 7 FILE WPIDS
L40 0 FILE JICST-EPLUS

TOTAL FOR ALL FILES

```
L41          44 RIORDAN N?/AU,IN

=> s (?tumour? or ?tumor? or ?cachexia?)(1)immune response and l41
L42           0 FILE MEDLINE
L43           0 FILE CAPLUS
L44           0 FILE BIOSIS
L45           0 FILE EMBASE
L46           0 FILE WPIDS
LEFT TRUNCATION IGNORED FOR '?TUMOUR?' FOR FILE 'JICST-EPLUS'
LEFT TRUNCATION IGNORED FOR '?TUMOR?' FOR FILE 'JICST-EPLUS'
LEFT TRUNCATION IGNORED FOR '?CACHEXIA?' FOR FILE 'JICST-EPLUS'
L47           0 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L48           0 (?TUMOUR? OR ?TUMOR? OR ?CACHEXIA?)(L) IMMUNE RESPONSE AND L41
Left truncation is not valid in the specified search field in the
specified file.  The term has been searched without left truncation.
Examples: '?TERPEN?' would be searched as 'TERPEN?' and '?FLAVONOID'
would be searched as 'FLAVONOID.'

If you are searching in a field that uses implied proximity, and you
used a truncation symbol after a punctuation mark, the system may
interpret the truncation symbol as being at the beginning of a term.
Implied proximity is used in search fields indexed as single words,
for example, the Basic Index.

=> s (?tumour? or ?tumor? or ?cachexia?) and l41
L49           4 FILE MEDLINE
L50           6 FILE CAPLUS
L51           5 FILE BIOSIS
L52           4 FILE EMBASE
L53           4 FILE WPIDS
LEFT TRUNCATION IGNORED FOR '?TUMOUR?' FOR FILE 'JICST-EPLUS'
LEFT TRUNCATION IGNORED FOR '?TUMOR?' FOR FILE 'JICST-EPLUS'
LEFT TRUNCATION IGNORED FOR '?CACHEXIA?' FOR FILE 'JICST-EPLUS'
L54           0 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L55          23 (?TUMOUR? OR ?TUMOR? OR ?CACHEXIA?) AND L41
Left truncation is not valid in the specified search field in the
specified file.  The term has been searched without left truncation.
Examples: '?TERPEN?' would be searched as 'TERPEN?' and '?FLAVONOID'
would be searched as 'FLAVONOID.'

If you are searching in a field that uses implied proximity, and you
used a truncation symbol after a punctuation mark, the system may
interpret the truncation symbol as being at the beginning of a term.
Implied proximity is used in search fields indexed as single words,
for example, the Basic Index.

=> dup rem l55
PROCESSING COMPLETED FOR L55
L56           8 DUP REM L55 (15 DUPLICATES REMOVED)

=> d 1-8 cbib abs
```

L56 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 1
2001:300532 Document No. 134:305295 Treatment of cancer with cytokines and other molecules from the growth medium of human monocytes. **Riordan, Neil**; Riordan, Hugh D. (The Center for the Improvement of Human Functioning, International, Inc., USA). PCT Int. Appl. WO 2001028573 A2 20010426, 16 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US41461 20001023. PRIORITY: US 1999-PV160664 19991021.

AB Treatment of **tumors**, including their metastases, is described. Retrieved cytokines and other mols. from the growth medium of human monocytes stimulated ex vivo with gamma globulin, or other immune stimulators are employed for cancer therapy. Efficacy of monocyte conditioned medium (cytokines and other mols. found in growth medium of cultured monocytes exposed to gamma globulin) in the treatment of different patients suffering from cancer is described.

L56 ANSWER 2 OF 8 MEDLINE DUPLICATE 2
2001311561 Document Number: 21278286. PubMed ID: 11384106. Cytotoxicity of ascorbate, lipoic acid, and other antioxidants in hollow fibre in vitro **tumours**. Casciari J J; **Riordan N H**; Schmidt T L; Meng X L; Jackson J A; Riordan H D. (Bio-Communications Research Institute, Center for the Improvement of Human Functioning International, 3100 North Hillside Avenue, Wichita, KS 67219, USA.) BRITISH JOURNAL OF CANCER, (2001 Jun 1) 84 (11) 1544-50. Journal code: AV4; 0370635. ISSN: 0007-0920. Pub. country: Scotland: United Kingdom. Language: English.

AB Vitamin C (ascorbate) is toxic to **tumour** cells, and has been suggested as an adjuvant cancer treatment. Our goal was to determine if ascorbate, in combination with other antioxidants, could kill cells in the SW620 hollow fibre in vitro solid **tumour** model at clinically achievable concentrations. Ascorbate anti-cancer efficacy, alone or in combination with lipoic acid, vitamin K3, phenyl ascorbate, or doxorubicin, was assessed using annexin V staining and standard survival assays. 2-day treatments with 10 mM ascorbate increased the percentage of apoptotic cells in SW620 hollow fibre **tumours**. Lipoic acid synergistically enhanced ascorbate cytotoxicity, reducing the 2-day LC(50)in hollow fibre **tumours** from 34 mM to 4 mM. Lipoic acid, unlike ascorbate, was equally effective against proliferating and non-proliferating cells. Ascorbate levels in human blood plasma were measured during and after intravenous ascorbate infusions. Infusions of 60 g produced peak plasma concentrations exceeding 20 mM with an area under the curve (24 h) of 76 mM h. Thus, **tumoricidal** concentrations may be achievable in vivo. Ascorbate efficacy was enhanced in an additive fashion by phenyl ascorbate or vitamin K3. The effect of ascorbate on doxorubicin efficacy was concentration dependent; low doses were

protective while high doses increased cell killing. Copyright 2001 Cancer Research Campaign.

L56 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 3
2000:592551 Document No. 133:172167 Use of lipoic acid combination with ascorbic acid in the treatment of cancer. Casciari, Joseph; **Riordan, Neil H.** (Center for the Improvement of Human Functioning International, Inc., USA). PCT Int. Appl. WO 2000048594 A1 20000824, 14 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US3656 20000211. PRIORITY: US 1999-249872 19990216.

AB Lipoic acid and/or its water sol. salt is used to treat cancer, alone or in combination with ascorbic acid (vitamin C). Alone or in combination, it was shown to be effective on in vitro **tumors** and mouse **tumors**. The agents can be administered safely, and have been used effectively in case studies.

L56 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 4
2000:454206 Document No. 133:79320 High molecular weight extracts of Convolvulus arvensis field (field bindweed). Meng, Xiaolong; Riordan, Hugh D.; **Riordan, Neil H.** (The Center for the Improvement of Human Functioning, Int'l., Inc., USA). U.S. US 6083510 A 20000704, 5 pp.
(English). CODEN: USXXAM. APPLICATION: US 1999-249874 19990216.

AB A purified bindweed ext. is used to inhibit the growth of **tumor** cells, inhibit the growth of blood vessels, and enhance immune function. The bindweed ext. is prepd. by removing toxic low mol. wt. components of Convolvulus arvensis. High mol. wt. exts. of Convolvulus arvensis were isolated and characterized. The high mol. wt. exts. lt 200 .mu.g/egg inhibited angiogenesis in chicken egg chorioallantoic membranes by 73% and
at a dose of 14 mg inhibited **tumor** growth in mice by 77%..

L56 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 5
1997:411073 Document No. 127:29082 Therapeutic method using ascorbate i.v. infusion for the treatment of cancer. **Riordan, Neil H.**; Riordan, Hugh D. (Center for the Improvement of Human Functioning Int'l, Inc., USA). U.S. US 5639787 A 19970617, 6 pp. (English). CODEN: USXXAM. APPLICATION: US 1995-397663 19950228.

AB A method of treating cancer in a patient is provided which includes raising and maintaining the concn. of ascorbic acid, or ascorbate, in the patient's plasma to at least the level expected to be toxic to an in vitro
culture of cells of the type of cancer being treated, the required plasma ascorbate levels being achieved and maintained using long term i.v. infusions of large amts. of ascorbate, with or without ascorbate cytotoxicity effectiveness enhancing or **tumor** site delivery and absorption enhancing agents.

L56 ANSWER 6 OF 8 MEDLINE DUPLICATE 6
96396827 Document Number: 96396827. PubMed ID: 8803930. The paradoxical role of lipid peroxidation on carcinogenesis and **tumor** growth: a commentary. Gonzalez M J; **Riordan N H.** (University of Puerto Rico, School of Public Health, San Juan, Puerto Rico.) MEDICAL HYPOTHESES, (1996 Jun) 46 (6) 503-4. Journal code: M0M; 7505668. ISSN: 0306-9877. Pub. country: ENGLAND: United Kingdom. Language: English.
AB Lipid peroxidation has been shown to both enhance carcinogenesis and to have an anticarcinogenic effect. This paradox is of great relevance to the fields of free radical biology, biochemistry, pathology, nutrition and oncology among others and needs to be addressed. A proper understanding of this issue can be a key to more effective treatment of malignant **tumors** in the near future.

L56 ANSWER 7 OF 8 MEDLINE DUPLICATE 7
95333962 Document Number: 95333962. PubMed ID: 7609676. Intravenous ascorbate as a **tumor** cytotoxic chemotherapeutic agent. **Riordan N H;** Riordan H D; Meng X; Li Y; Jackson J A. (Project RECNAC, Bio-Communications Research Institute, Wichita, Kansas 67219, USA.) MEDICAL HYPOTHESES, (1995 Mar) 44 (3) 207-13. Journal code: M0M; 7505668. ISSN: 0306-9877. Pub. country: ENGLAND: United Kingdom. Language: English.
AB Ascorbic acid and its salts (AA) are preferentially toxic to **tumor** cells in vitro and in vivo. Given in high enough doses to maintain plasma concentrations above levels that have been shown to be toxic to **tumor** cells in vitro, AA has the potential to selectively kill **tumor** cells in a manner similar to other **tumor** cytotoxic chemotherapeutic agents. Most studies of AA and cancer to date have not utilized high enough doses of AA to maintain **tumor** cytotoxic plasma concentrations of AA. Data are presented which demonstrate the ability to sustain plasma levels of AA in humans above levels which are toxic to **tumor** cells in vitro and suggests the feasibility of using AA as a cytotoxic chemotherapeutic agent.

L56 ANSWER 8 OF 8 MEDLINE DUPLICATE 8
94354626 Document Number: 94354626. PubMed ID: 8074495. Improved microplate fluorometer counting of viable **tumor** and normal cells. Riordan H D; **Riordan N H;** Meng X; Zhong J; Jackson J A. (Project RECNAC, Bio-Communications Research Institute, Wichita, Kansas 67219.) ANTICANCER RESEARCH, (1994 May-Jun) 14 (3A) 927-31. Journal code: 59L; 8102988. ISSN: 0250-7005. Pub. country: Greece. Language: English.
AB An improved method has been developed to count cells in situ based on the measurement of esterase activity with carboxyfluorescein diacetate. This sensitive, semiautomated microplate fluorometer assay was able to estimate viable cell numbers over a range of 5 x 10(2) to 2.6 x 10(5) cells/well in a **tumor** cell line. Sensitivity to 10(3) was demonstrated in two other cell lines. Sub- and supranormal fluorescence events which can be responsible for unreliable readings when using a fluorescence assay for

cell counting were quantified in a menadione (cytotoxic agent)/U-87 MG (cell line) model. There was a close correlation between the fluorometer method and Coulter counter method for two different **tumor** cell lines when this method was performed on cells after sub- and supranormal fluorescence events had ceased.

```
=> s l41 not l55
L57           2 FILE MEDLINE
L58           4 FILE CAPLUS
L59           5 FILE BIOSIS
L60           7 FILE EMBASE
L61           3 FILE WPIDS
L62           0 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L63          21 L41 NOT L55

=> dup rem l63
PROCESSING COMPLETED FOR L63
L64           16 DUP REM L63 (5 DUPLICATES REMOVED)

=> d cbib abs 1-16

L64  ANSWER 1 OF 16  CAPLUS  COPYRIGHT 2001 ACS
2001:561859  Retrospective analysis of the effects of low-dose, high frequency
     human growth hormone on serum lipids and prostate specific antigen.
     Chein, Edmund; Gonzalez, Michael J.; Riordan, Neil H. (Palm
     Springs Life Extension Institute, Palm Springs, CA, 92262, USA). J. Am.
     Aging Assoc., 24(2), 59-62 (English) 2001. CODEN: JAAABY. Publisher:
     Journal of the American Aging Association.
AB   Elevated serum total cholesterol (TC) and triglycerides (TG) are risk
     factors for atherosclerosis and ischemic heart disease. Adult growth
     hormone deficiency (AGHD) is assocd. with elevated TC and TG. Many
     treatment protocols for AGHD use relatively high doses of growth hormone
     (GH) given at low frequency, which is assocd. with increased incidences
of
     edema, joint pains, and carpal tunnel syndrome. We have treated > 2200
     patients using a low-dose high frequency (LDHF) dosing regimen of GH
which
     results in similar beneficial subjective responses, and fewer of the
     side-effects assocd. with the higher-dosage treatment at a substantial
     cost savings. Clin., in addn. to increased insulin-like growth factor I
     (IGF-I), we obsd. lower TG and TC levels and no elevation of prostate
     specific antigen levels in treated patients. A retrospective anal. of
     IGF-I, TG, TC, and PSA data from our patient population was performed to
     test our hypothesis that pos. objective responses of IGF-I, TG, and TC
     occur and that elevation of PSA does not occur in response to LDHF dosing
     regimen of GH. The mean duration of treatment of the analyzed data
ranged
     from 181 to 259 days. The mean plasma IGF-I level rose significantly
     (p<.00001) to a level 37% greater than baseline with treatment. TC and
TG
     decreased significantly (p<.001) in those patients with elevated baseline
     values, and did not change significantly in those with normal baseline
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values. PSA concns. decreased non-significantly during treatment, and few cases of edema, joint pain, or carpal tunnel were reported. Treatment of AGHD using the LDHF dosing regimen of GH resulted in significant increases in IGF-I, significant redns. in TC and TG levels in patients with elevated baseline values, no increase in PSA concns., and fewer side effects than other dosing regimens.

L64 ANSWER 2 OF 16 MEDLINE
2001382429 Document Number: 21190207. PubMed ID: 11293891. Integrative medicine: a paradigm shift in medical education and practice. Gonzalez M J; Miranda-Massari J R; Mora E M; Cruzado N A; Jimenez I; Rosa M; Matos Vera M I; Santiago C; Roman-Eyxarch M I; Rodriguez J R; Perez Cortes C; **Riordan N H**; Riordan H D; Ricart C M. (InBioMed Project, Nutrition Program, Department of Human Development, School of Public Health, University of Puerto Rico, Medical Sciences, Campus.) PUERTO RICO HEALTH SCIENCES JOURNAL, (2000 Dec) 19 (4) 389-92. Journal code: QJF; 8303541. ISSN: 0738-0658. Pub. country: Puerto Rico. Language: English.
AB The use of alternative/complementary medicine has been increasing considerably. Conventional medicine must begin to address issues related to the use, safety, regulation, research and education of alternative/complementary medicine. Integrative medicine combines conventional medicine and alternative complementary practices. Integrative medicine is an innovative approach to medicine and medical education. It involves the understanding of the interaction of the mind, body and spirit and how to interpret this relationship in the dynamics of health and disease. Integrative medicine shifts the orientation of the medical practice from disease based approach to a healing based approach. It does not reject conventional medicine nor uncritically accepts unconventional practices. Integrative medicine is an effective, more fulfilling human approach to medicine based on the benefit of the patient by following good medicine practices in a scientific manner.

L64 ANSWER 3 OF 16 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
2001035482 EMBASE Clinical and experimental experiences with intravenous vitamin C. **Riordan N.H.**; Riordan H.D.; Casciari J.P.. N.H. Riordan, Bio-Communications Res. Institute, 3100 N. Hillside Ave, Wichita, KS 67219, United States. Journal of Orthomolecular Medicine 15/4 (201-213) 2000.
Refs: 6.
ISSN: 0317-0209. CODEN: JORMEI. Pub. Country: Canada. Language: English. Summary Language: English.
AB For the purposes of this paper reference to ascorbic acid or vitamin C refers to sodium ascorbate. All in vitro studies described herein used sodium ascorbate. All intravenous vitamin C references herein refer to the use of vitamin C for injection produced by Steris Laboratories, or American Regent laboratories; both are ascorbic acid buffered to a pH range of 5.5 to 7.0 by sodium hydroxide and/or sodium bicarbonate.

L64 ANSWER 4 OF 16 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 1
1999:90231 Document No. 130:129783 Skin treatment system affecting the aging
process. **Riordan, Neil H.** (USA). U.S. US 5866142 A 19990202, 7 pp. (English). CODEN: USXXAM. APPLICATION: US 1996-586029 19960113.
AB A skin treatment system comprises histidine acting as a divalent cation chelator and exfoliant, pyridoxine and pantothenic acid and N-acetyl-D-glucosamine for increasing prodn. of hyaluronic acid, superoxide dismutase and cysteine and vitamin E for decreasing the oxidative degrdn. of the hyaluronic acid, and pyrrolidonecarboxylic acid or chem. salts thereof, and hyaluronic acid, or chem. salts thereof for providing increased hydration of the skin.

L64 ANSWER 5 OF 16 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
97329685 EMBASE Document No.: 1997329685. Antioxidants and cancer: A brief discussion on controversies, contradictions and paradoxes. Gonzalez M.J.; **Riordan N.H.**; Matos M.I.; Arguelles M.. M.J. Gonzalez, University of Puerto Rico, Medical Sciences Campus, Department of Human Development, PO Box 365067, San Juan, PR 00936-5067, Puerto Rico. Journal of Orthomolecular Medicine 12/3 (145-148) 1997.
Refs: 23.
ISSN: 0317-0209. CODEN: JORMEI. Pub. Country: Canada. Language: English. Summary Language: English.
AB Antioxidants have been associated with cancer prevention. Since this association was established, a plethora of controversies, contradictions and paradoxes have arisen. In this article we will try to provide an insight into the complexity involved with antioxidants, pro-oxidants and cancer in the free radical biology area.

L64 ANSWER 6 OF 16 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
97251792 EMBASE Document No.: 1997251792. Urinary pyrrole in health and disease. Jackson J.A.; Riordan H.D.; Neathery S.; **Riordan N.H.**. Dr. J.A. Jackson, Department of Medical Technology, Wichita State University, Wichita, KS 67206-0043, United States. Journal of Orthomolecular Medicine 12/2 (96-98) 1997.
Refs: 16.
ISSN: 0317-0209. CODEN: JORMEI. Pub. Country: Canada. Language: English.

L64 ANSWER 7 OF 16 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1996-068190 [07] WPIDS
CR 1994-248395 [30]
AB US 5480613 A UPAB: 19960222
Kit for detecting Dientamoeba fragilis in samples including faeces or intestinal mucosa comprises: (a) a vessel contg. isotonic saline for holding the sample, and which may be centrifuged to provide (via converging sidewalls) a region with a sediment contg. D. fragilis; (b) an acridine cpd. (I) as staining agent present in the sample vessel or a separate vessel; and (c) means for viewing a portion of the stained coloured sediment to detect a separate colour indicating the presence of the organism.
ADVANTAGE - The method reliably detects the intestinal parasite D. fragilis, esp. in human faecal samples.
Dwg.0/14

L64 ANSWER 8 OF 16 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
96251383 EMBASE Document No.: 1996251383. Intravenous vitamin C in a terminal
cancer patient. **Riordan N.**; Jackson J.A.; Riordan H.D.. Center for the Improvement, Human Functioning International, Inc, 3100 N. Hillside,Wichita, KS 67219, United States. Journal of Orthomolecular Medicine 11/2 (80-82) 1996.
ISSN: 0317-0209. CODEN: JORMEI. Pub. Country: Canada. Language: English.

L64 ANSWER 9 OF 16 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 2
1996:403518 Document No. 125:83127 Antioxidants and pro-oxidants: a commentary about their apparent discrepant role in carcinogenesis. Gonzalez, Michael J.; Lopez, Delisabel; Argulies, Mercedes; **Riordan, Niel H.** (School of Public Health, University of Puerto Rico, San Juan, 00936, P. R.). Age (Chester, Pa.), 19(1), 17-18 (English) 1996.
CODEN: AGEEDB. ISSN: 0161-9152.
AB A review with 8 refs.

L64 ANSWER 10 OF 16 CAPLUS COPYRIGHT 2001 ACS
1996:81599 Document No. 124:111725 Method for detecting intestinal pathogen Dientamoeba fragilis. **Riordan, Neil H.** (Center for the Improvement of Human Functioning International, Inc., USA). PCT Int. Appl. WO 9530767 A1 19951116, 25 pp. DESIGNATED STATES: W: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KG, KP, KR, KZ, LK, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1994-US5113 19940509.
AB A method and app. for producing detectable intestinal parasites are disclosed. The method comprises obtaining an intestinal mucosa sample (e.g. feces) having intestinal parasites, such as Dientamoeba fragilis; and contacting the obtained intestinal mucosa sample with an acridine base
compd. (e.g. acridine orange and/or acridine yellow, etc.) such that the intestinal parasites become differentially stained and detectable by a human eye when viewed through a fluorescence microscope. The app. includes a kit or the like which includes at least one vessel or vial. Preferably, two vials are contained within the kit with one vial having an
isotonic salt soln. comprising a salt, such as sodium chloride, potassium phosphate, etc., and the other vial contg. an acridine biol. staining compd.

L64 ANSWER 11 OF 16 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
95249964 EMBASE Document No.: 1995249964. High dose intravenous vitamin C and
long time survival of a patient with cancer of head of the pancreas. Jackson J.A.; Riordan H.D.; Hunninghake R.E.; **Riordan N.**. Graduate School, Wichita State University,Wichita, KS 67260-0004, United States. Journal of Orthomolecular Medicine 10/2 (87-88) 1995.
ISSN: 0317-0209. CODEN: JORMEI. Pub. Country: Canada. Language: English.

L64 ANSWER 12 OF 16 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1994-248395 [30] WPIDS
CR 1996-068190 [07]

AB US 5334509 A UPAB: 19960227
Determining if Dientamoeba fragilis (Df) is present in a faecal material from a human being comprises (a) contacting faecal sample with acridine soln. in a wt. ratio of 1:10 to 10:1 so that if Df is present in faecal sample, Df becomes stained with first colour, and if residual faecal material is present in faecal sample, residual faecal material becomes stained with second colour, acridine soln. comprising aq. soln. and 0.4-100 mcg/ml of acridine biological staining cpd.; and (c) viewing through fluorescence microscope the obtd. faecal sample after being contacted with the acridine soln. and detecting presence of first colour, signifying presence of Df in the sample, and further detecting presence of
second colour, signifying presence of residual faecal material in sample.
USE/ADVANTAGE - Used for detecting pathogenic Df protozoa which is associated with diarrhoea, abdominal pains, pruritus and loose stools. The
acridine biological staining cpd. provides for easily differentiation and subsequent ready identification of Df.
Dwg.0.14

L64 ANSWER 13 OF 16 MEDLINE DUPLICATE 3
90341481 Document Number: 90341481. PubMed ID: 2116643. Underreporting of
minority AIDS deaths in San Francisco Bay area, 1985-86. Lindan C P; Hearst N; Singleton J A; Trachtenberg A I; **Riordan N M**; Tokagawa D A; Chu G S. (Center for AIDS Prevention Studies (CAPS), University of California, San Francisco.) PUBLIC HEALTH REPORTS, (1990 Jul-Aug) 105 (4)
400-4. Journal code: QJA; 9716844. ISSN: 0033-3549. Pub. country: United States. Language: English.
AB A disproportionately high number of AIDS cases in the United States involve members of racial minorities. Even so, AIDS deaths of minority members may be undercounted. The completeness of reporting of AIDS deaths to the California AIDS Registry (ARS) among Hispanics, blacks, and whites in 1985 and 1986 from the San Francisco Bay Area was investigated. Death certificates listing AIDS as a cause of death or associated condition were
identified and cross-checked with cases reported to ARS, current to December 1988. Death certificates were checked by hand for racial or ethnic classification using a definition of Hispanic based on information available on certificates. Three causes of undercounting in ARS were identified: a death was not reported as an AIDS case at all, an AIDS case was reported to ARS but the person was listed as still living, or an AIDS death was reported to ARS with a different racial or ethnic classification. The proportion of cases not reported at all was similar for all three racial-ethnic groups (5-8 percent). The proportion of deaths
reported for persons listed in the registry as still living was 12 percent
for Hispanics and 9 percent for blacks, compared with 5 percent for whites. For Hispanics, under-counting was largely due to ethnic misclassification. Twenty percent of Hispanics had been counted as white in the AIDS registry. In comparison, 4 percent of blacks and 1 percent of whites were misclassified by race. AIDS deaths among blacks and Hispanics may be undercounted, even in an area with good AIDS surveillance systems.

This suggests that overrepresentation of minorities among AIDS cases in the United States may be even greater than indicated by current reporting data.

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1989:460576 Document No.: BR37:93220. DEMOGRAPHIC PROFILES OF SAN FRANCISCO BAY AREA USA BLACK AND LATIN AIDS DEATHS 1985-1986. HAYNES K; CHU G; **RIORDAN N**; TOKUGAWA D; FULLILOVE R. MULTICULTURAL INQUIRY AND RES. ON AIDS COMPONENT OF UCSF CENT. FOR AIDS PREVENTION STUDIES AND BAYVIEW-HUNTER'S POINT FOUND., SAN FRANCISCO, CALIF., USA.. MORISSET, R. A. (ED.). VE CONFERENCE INTERNATIONALE SUR LE SIDA: LE DEFI SCIENTIFIQUE ET SOCIAL; V INTERNATIONAL CONFERENCE ON AIDS: THE SCIENTIFIC AND SOCIAL CHALLENGE; MONTREAL, QUEBEC, CANADA, JUNE 4-9, 1989. 1262P. INTERNATIONAL DEVELOPMENT RESEARCH CENTRE: OTTAWA, ONTARIO, CANADA. ILLUS. PAPER. (1989)
0 (0), 747. ISBN: 0-662-56670-X. Language: English.

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1989:417612 Document No.: BR37:73075. UNDERREPORTING OF MINORITY AIDS DEATHS IN THE SAN FRANCISCO BAY AREA CALIFORNIA USA 1985-1986. CHU G; TRACHTENBERG A I; HEARST N; **RIORDAN N**; CREEGER J; SORENSEN J; ET AL. CENT. AIDS PREVENTION STUDIES, UNIV. CALIF., SAN FRANCISCO, CALIF.. MORISSET, R. A. (ED.). VE CONFERENCE INTERNATIONALE SUR LE SIDA: LE DEFI SCIENTIFIQUE ET SOCIAL; V INTERNATIONAL CONFERENCE ON AIDS: THE SCIENTIFIC
AND SOCIAL CHALLENGE; MONTREAL, QUEBEC, CANADA, JUNE 4-9, 1989. 1262P. INTERNATIONAL DEVELOPMENT RESEARCH CENTRE: OTTAWA, ONTARIO, CANADA. ILLUS.
PAPER. (1989) 0 (0), 55. ISBN: 0-662-56670-X. Language: English.

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1988:410284 Document No.: BR35:73259. IMPLICATIONS OF PREMATURE OVARIAN FAILURE FOR THE ADOLESCENT FEMALE A CASE REPORT. **RIORDAN N**; MAMMEL K. CHILDREN'S HOSP., DENVER, COLO.. ANNUAL MEETING OF THE SOCIETY FOR ADOLESCENT MEDICINE, MARCH 1988. J ADOLESC HEALTH CARE. (1988) 9 (3), 262. CODEN: JAHCD9. Language: English.

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